CME CREDIT

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Managing genital herpes infections in pregnancy

ABSTRACT

Genital herpes is common and is becoming more so, with a seroprevalence of 25% in middle class primary care settings. Primary genital herpes in pregnancy most often is subclinical, but it also can cause severe illness. Further, active genital herpes at the time of vaginal delivery poses significant risk of neonatal infection, especially if the mother acquired the infection in the third trimester. It is important to prevent genital herpes acquisition in pregnancy and to diagnose recurrent genital herpes to prevent neonatal herpes.

KEY POINTS

Up to 2% of women may acquire herpes simplex virus (HSV) infection during pregnancy, and the risk rises to about 20% if the woman's partner is HSV-positive.

Neonatal herpes can have severe consequences such as encephalitis and neonatal death.

Antiviral therapy is indicated for primary HSV infection in pregnancy and can be used to prevent recurrent genital lesions at term.

Women who have genital herpes lesions when they go into labor should undergo cesarean delivery to decrease the risk of neonatal herpes.

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HERPES SIMPLEX VIRUS (HSV) infection is common and can endanger the health of the mother and fetus during pregnancy. Diagnosing and managing genital herpes before or during pregnancy (or better yet, preventing it) can improve the mother's health and reduce the chance of transmission from mother to neonate.

This is a job for primary care physicians. Most pregnancies in the United States are unplanned, and although prenatal counseling is advised, very few women see an obstetrician before conception. Therefore, primary care providers are in a unique position to provide important preconception information to their female patients of reproductive age.

This article will review how to counsel women about HSV infections and how to manage them during pregnancy.

GENITAL HERPES IS VERY COMMON

Genital herpes is a common viral sexually transmitted disease, and it is increasing in prevalence. Two types of HSV can cause it, HSV-1 and HSV-2 (discussed below).

The third National Health and Nutrition Examination Survey (1988–1994) found that 22% of the general US population older than age 12 had antibodies to HSV-2, a 30% increase since 1976.[1–3] In another survey,[4] 25.5% of patients in suburban primary care offices were seropositive for HSV-2.

Between 20% and 30% of pregnant women have antibodies to HSV-2,[5] and 10% of pregnant women are at risk of acquiring the disease from their partners because they are HSV-2-seronegative and their partners are HSV-2-seropositive.[6] Overall, 2% of women

in a general obstetrics practice acquire HSV during pregnancy,[5] but for HSV-2-seronegative women with HSV-2-seropositive partners, the risk is approximately 20%.[6,7]

Nevertheless, genital herpes is underdiagnosed, mainly because its manifestations are usually subclinical. Remarkably, up to 90% of people with genital herpes do not know that they are infected.[1,8–10] Most sexual transmission of HSV occurs during episodes of subclinical reactivation in people who do not know they are infected. Among those with known infection, 70% of transmissions occur during periods of asymptomatic viral shedding.[8,11–14]

Virtually all HSV-2-seropositive people intermittently shed HSV from the genital mucosa, and most have mild, recurrent symptoms.[15] Many women, including pregnant women, attribute these mild genital symptoms to recurrent yeast or urinary tract infections, bacterial vaginitis, and allergies to condoms, semen, spermicides, and panty hose. Many men think they have "jock itch," zipper burns, condom allergies, penile acne, bike seat rubs, or bug bites.[10,15–17]

Up to 90% of people with genital herpes do not know that they are infected

HSV-1 infection rarely recurs—except in pregnancy

HSV-1 has emerged as a major cause of genital herpes, particularly in the college-age population, in which up to 80% of new cases are now caused by HSV-1.[18–20] Epidemiologic studies suggest that oral-genital contact is a risk factor for genital HSV-1.[21]

While the clinical presentation of initial genital herpes is the same for HSV-1 and HSV-2, they differ in prognosis, making it necessary to distinguish the two. Genital HSV-1 infection rarely recurs symptomatically or asymptomatically after the first year of infection.[22,23] Notably, however, HSV-1 reactivations may occur after mid-pregnancy, when women are relatively immunosuppressed. In contrast, genital HSV-2 continues to recur, often frequently, for many years.[24]

CLINICAL CHARACTERISTICS OF HSV IN PREGNANCY

Approximately 70% of newly acquired HSV infections in pregnant women are asymptomatic or unrecognized.[5,6] The remaining 30% have clinical presentations that range from minimal lesions and mild discomfort to widespread genital lesions associated with severe local pain, dysuria, sacral paresthesia, tender regional lymph node enlargement, fever, malaise, and headache. Aseptic meningitis occurs less frequently, and disseminated disease is rare.

Similarly, most reactivations of genital herpes are unrecognized.[25] The spectrum of clinically evident recurrent episodes varies from very mild to severe symptoms that are clinically indistinguishable from a primary infection.[5,26] Therefore, providers should consider HSV when caring for women with subtle genital symptoms or with unusually severe illness in pregnancy, as both ends of the disease spectrum are easy to miss.

Disseminated HSV is rare but serious

Rarely, a new or reactivated HSV infection in pregnancy can cause disseminated disease with hepatitis, encephalitis, or pneumonitis. Prompt diagnosis and treatment are critical in such cases.

Disseminated HSV should be considered in pregnant women who report fever and a flu-like prodrome that progresses to pneumonitis, hepatitis, or encephalitis, with or without characteristic skin lesions, especially in mid-pregnancy.[27,28] (Mucocutaneous lesions may appear late or not at all and should not be relied upon for diagnosis.[29])

HSV hepatitis typically presents in the third trimester of pregnancy with fever, anicteric hepatic dysfunction, markedly elevated aminotransferase levels, and abdominal tenderness.

One should consider HSV encephalitis in any pregnant woman with new-onset seizures, change in mental status, or fever and headache.[30] The diagnosis is confirmed by polymerase chain reaction (PCR) testing of the cerebrospinal fluid.

Consider HSV endometritis if a postpartum woman has persistent fever despite antibiotic and anticoagulant therapy. The diagnosis should be confirmed with an endometrial biopsy for HSV PCR or culture.[31,32]

Laboratory testing confirms HSV infection

In all cases, the diagnosis of genital HSV

TABLE 1

Recommended glycoprotein G-based type-specific tests for herpes simplex virus (HSV) antibodies

TEST	SENSITIVITY (%)*	SPECIFICITY (%)*	COLLECTION METHOD	TEST LOCATION	MEDIAN TIME TO SEROCONVERSION
HerpeSelect HSV-1 ELISA† (enzyme-linked immunosorbent assay)	96	95.2	Blood draw	Laboratories (best for high-volume laboratories)	21–23 days
HerpeSelect HSV-2 ELISA†	100	96.1	Blood draw	Laboratories (best for high-volume laboratories)	21–23 days
HerpeSelect HSV-1 Immunoblot†	100	93.1	Blood draw	Laboratories (best for low-volume laboratories)	Unknown
HerpeSelect HSV-2 Immunoblot†	100	93.7	Blood draw	Laboratories (best for low-volume laboratories)	Unknown
Biokit HSV-2 Rapid Test‡	93–96	94–97	Finger stick	Provider's office	13 days
Captia HSV-1 ELISA§	Unknown	Unknown	Blood draw	Laboratories	14 days
Captia HSV-2 ELISA§	96	98	Blood draw	Laboratories	14 days
Western blot (HSV-1 and HSV-2)	> 99	> 99	Blood draw	U. of Washington virology laboratory	42–47 days

*The sensitivity and specificity of the HerpeSelect ELISA, Immunoblot, Biokit HSV-2, and Captia ELISA were determined by comparison to Western blot. The sensitivity and specificity of the Western blot was determined using men and women (not selected for pregnancy status) with symptomatic established infections. Results for Captia HSV-1 ELISA have been determined but are not yet published.
†Focus Diagnostics; Cypress, CA
‡Biokit USA; Lexington, MA; also known as Sure-Vue HSV-2 from Fisher HealthCare
§Trinity Biotech, Bray, County Wicklow, Ireland

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infection requires laboratory confirmation, although antiviral therapy can be started on the basis of clinical presentation (and *must* be started on this basis, pending laboratory results, in severe cases).

HSV culture is routinely performed in patients who present with genital ulcers or other mucocutaneous lesions. However, the sensitivity of HSV culture is relatively low, especially in recurrent lesions, and declines rapidly after a day or two as lesions begin to heal. In addition, the specimens require careful handling with rapid transportation to the laboratory.

PCR assays for HSV DNA are more sensitive, do not require special handling, have become more widely available, and can be used instead of viral culture.[33–36] Specimens for PCR can be collected in the same manner as for culture and simply labeled as "HSV PCR with typing" on the laboratory request. (Typing, ie, determining whether HSV-1 or HSV-2 is the cause of the infection, should be requested with either PCR or viral culture.)

Serologic testing. A negative result on culture or PCR does not rule out HSV infection, as viral shedding is intermittent. Thus, type-specific HSV serologic testing is an important diagnostic tool for women whose culture or PCR results are negative or who do not have lesions at the time of presentation.[37] If you suspect that the patient has a new HSV infection but if culture or PCR fails to isolate the virus from the lesion and her serologic test is negative, the serologic test should be repeated in 6 weeks.

Classified by test results

On the basis of the results of culture, PCR, and serologic tests, genital HSV infections are classified as:

Primary infection (the culture or PCR assay is positive for HSV-1 or HSV-2, but serologic tests are negative)

Nonprimary first-episode disease (the culture or PCR assay is positive for HSV-2, and serologic tests are positive for HSV-1)

Recurrent or reactivation disease (the culture or PCR assay is positive for HSV-1 or HSV-2, and serologic tests are positive for HSV of the same serotype).

These categories are important in pregnancy, as the risk of perinatal HSV transmission varies accordingly.

TYPE-SPECIFIC HSV SEROLOGIC ASSAYS

Immunoglobulin G (IgG) antibodies to HSV appear during the first several weeks after infection, increase during the subsequent 8 to 12 weeks, and persist indefinitely. The response to HSV-2 is distinguishable from that to HSV-1 because the surface glycoprotein G differs in size and epitope content between the two HSV types.[38]

Consider HSV in women with subtle genital symptoms or with unusually severe illness in pregnancy

Serologic assays that detect IgG antibodies to the HSV-1 glycoprotein G (gG1) and the HSV-2 glycoprotein G (gG2), or gG-based HSV assays, are commercially available (TABLE 1). These assays should replace the non-gG based HSV assays (many of which are still marketed as "type-specific"), which are in widespread use and provide inaccurate results.[39]

Only tests that detect IgG are recommended. Tests that detect IgM HSV antibodies cannot reliably diagnose new infections because IgM levels may be elevated with reactivation disease.

All of the type-specific assays are comparable in performance to the Western blot.[9,40–45] The sensitivities of these tests for HSV-2 antibody vary from 93% to 100%, but false-negative results can occur, especially in the early stages of infection. The specificities of these assays are greater than 96%. Focus Diagnostics (Cypress, CA) is developing a second-generation enzyme-linked immunosorbent assay (ELISA) to increase the specificity of its HerpeSelect HSV-2 ELISA.

False-positive results can also occur, especially in patients unlikely to be infected. Repeat or confirmatory testing with a second gG-based test (eg, Biokit HSV-2, also known as Sure-Vue HSV-2) may be indicated in some settings, especially if recent acquisition of genital herpes is suspected or if the results of the HerpeSelect HSV-2 ELISA are indeterminate.[46]

HSV-2 antibody indicates genital infection because almost all HSV-2 infections are from genital-to-genital sexual contact. Most people with HSV-1 antibody have oral HSV infection acquired in childhood, which may be asymptomatic. However, HSV-1 antibody may also indicate genital HSV-1 infection, which can also be asymptomatic. Thus, the presence of HSV-1 antibody by itself is difficult to interpret in people without a history of oral or genital herpes.

TREATING SYMPTOMATIC HERPES IN PREGNANCY

Primary or first-episode HSV infection

Antiviral therapy is recommended for women with symptomatic primary or nonprimary first-episode HSV infection during pregnancy.[47] A 7-day course of oral antiviral medication shortens lesion healing time and reduces viral shedding.

Women with disseminated HSV, pneumonitis, hepatitis, or encephalitis should receive intravenous acyclovir (Zovirax) 5 to 10 mg/kg body weight every 8 hours until they clinically improve, and then they should receive oral antiviral therapy such as valacyclovir (Valtrex) 1.0 g twice a day, for at least 10 days of total therapy.[37] Antiviral therapy should be started as soon as the diagnosis is suspected rather than wait for laboratory confirmation. Early consultation with an infectious disease specialist also is recommended if disseminated HSV is suspected.

Seroconversion may be delayed when a first-episode HSV infection is treated with antiviral medications.[48]

Recurrent infection

Before labor, recurrent HSV infection does not appear to have an adverse effect on pregnancy outcome.[49] Therefore, treatment with

antiviral medication is indicated only to relieve maternal symptoms. A 2-to-5-day course of oral antiviral medication may shorten the symptomatic period.[37] For women with frequent or severe recurrences, daily suppressive therapy with antiviral medication may be indicated, especially after the first trimester.

NEONATAL HERPES CAN BE SERIOUS

Neonatal herpes is defined as the diagnosis of HSV infection within the first 28 days of life. It occurs in up to 1 per 3,200 live births in the Pacific Northwest,[50] with an estimated incidence of 1,500 cases in the United States annually.[51]

Classified by clinical manifestations

Neonatal HSV infection presents with a spectrum of disease that is classified based on clinical manifestations.

Skin, eye, and mouth disease. Neonates with skin, eye, and mouth disease rarely have viral dissemination or visceral involvement. Skin, eye, and mouth disease accounts for 45% of cases now that early antiviral therapy has become the norm.[52,53]

Central nervous system disease. Almost one third of neonates with HSV infection have central nervous system disease, characterized by seizures, lethargy, irritability, tremors, poor feeding, temperature instability, and bulging fontanelles.

Disseminated infection accounts for the remaining 25% of cases, involves multiple organ systems, and may result in death from severe coagulopathy, liver dysfunction, and pulmonary failure.[51]

Begin treatment promptly for neonatal herpes

PCR testing has improved the early diagnosis of neonatal herpes. However, if this diagnosis is suspected, treatment should be started promptly without waiting for the results of tests.

Intravenous acyclovir has reduced the rates of death and sickness among neonates with skin, eye, and mouth disease, but has not markedly reduced the morbidity associated with disseminated or central nervous system disease. Despite early intervention with high-dose antiviral therapy, 30% of infants with disseminated disease die, and 40% of survivors of central nervous system disease have severe neurologic damage.[51] Therefore, prevention of neonatal infection is critical.

HSV is most often transmitted to babies at birth

In more than 90% of cases of neonatal herpes, the baby acquired HSV during vaginal birth, from infected genital tract secretions.[50,54–56] The major sites of viral entry are the eyes, nasopharynx, or a traumatized scalp.

In rare cases, a fetus is infected in the uterus when the mother acquires a primary infection that spreads across the placenta or up the birth canal, or a neonate acquires HSV-1 after birth from close contact with someone with orolabial herpes or HSV-1 infection at another nongenital site such as the finger or the breast.[57]

The stage of maternal infection at the time of delivery affects the risk of neonatal infection. Overall, in 60% to 80% of cases of neonatal herpes, the mother acquired genital herpes in the third trimester of pregnancy.[5] Among women with HSV in the genital secretions at the time of labor, the risk of neonatal herpes is 30% to 50% if she has newly acquired genital herpes, compared with 3% if she has reactivation disease.[50,55,56] In contrast, the risk of neonatal transmission is 1 in 4,500 among HSV-2-seropositive women who are without symptoms of genital herpes at the time of labor.[55]

Despite early treatment, 30% of infants with disseminated HSV die

The reason for the difference in neonatal risk may be that mothers with newly acquired infection do not yet have HSV antibodies that, if present, would provide transplacental passive immunity to the neonate. Maternal seroconversion takes 8 to 12 weeks. In addition, women with primary infection are likely to have high titers of virus in their genital secretions for up to 18 months after the initial infection.[58]

Neonates exposed to genital HSV-1 at birth are more likely to become infected than those exposed to HSV-2, regardless of the stage of maternal infection.[50] Thirty-one percent of neonates exposed to genital HSV-1 at the time of delivery became infected, compared with 3% of those exposed to HSV-2 (odds ratio 34.8, 95% confidence interval

TABLE 2

Antiviral treatment of herpes simplex virus (HSV) infection in pregnancy

INDICATION	ACYCLOVIR	VALACYCLOVIR
Disseminated HSV	5–10 mg/kg body weight intravenously every 8 hours until clinical improvement is noted, then orally for at least 10 days of total therapy	
First clinical episode of HSV	400 mg by mouth three times a day for 7–14 days	1 g by mouth twice a day for 7–14 days
Recurrent episode of HSV	400 mg by mouth three times a day for 5 days	500 mg by mouth twice a day for 5 days
Suppressive therapy	400 mg by mouth two or three times a day, started in the 36th week of pregnancy until delivery	500 mg by mouth twice a day to delivery

3.6–335, adjusted for first episode vs reactivation HSV).[50] However, infants with HSV-1 infection are more likely than those with HSV-2 to develop skin, eye, and mouth disease and are less likely to develop central nervous system involvement.[59]

In 60% to 80% of cases of neonatal herpes, the mother acquired genital herpes in the third trimester

PREVENTING NEONATAL HERPES

Cesarean delivery for women with active herpes in labor

For women with genital lesions or prodromal symptoms that suggest genital herpes, cesarean delivery is recommended to prevent neonatal infection.[47] Cesarean delivery significantly decreases, but does not completely eliminate, the risk of neonatal HSV among women with HSV detected in genital secretions at the time of labor.[50] Cesarean delivery is more likely to prevent transmission of the virus if it is done before the membranes rupture.

Cesarean delivery is not indicated in women with genital herpes who do not have active genital lesions or prodromal symptoms at the time of labor.

Physical examination is still the main method to infer whether HSV is present in the genital tract at the time of labor. All women with known genital herpes should be asked about genital symptoms when they are admitted to the hospital in labor, and a thorough examination of the cervix, vagina, and vulva should be performed at that time.

Some specialists recommend cesarean delivery for some women with newly acquired HSV in the third trimester of pregnancy to reduce the risk of neonatal herpes, regardless of symptoms or signs at the time of labor. Others recommend treatment with acyclovir followed by suppressive therapy for the remainder of the pregnancy. Then, if type-specific antibodies are present by the time of delivery and the woman is without lesions, vaginal delivery is allowed.

We believe that the latter approach is risky because suppressive therapy may not completely eliminate viral shedding and because although type-specific antibodies are detectable, they may not provide sufficient passive immunity if quantities are low.

Antiviral suppressive therapy

In women with symptomatic genital herpes, antiviral suppressive medication, started in the 36th week of pregnancy, reduced the rates of cesarean delivery for lesions and positive viral culture and PCR tests at the time of delivery.[60–67]

Although a study to prove that suppressive therapy prevents neonatal herpes is not feasible, it is reasonable to prescribe suppressive therapy to women with symptomatic recurrent genital herpes to avoid the need for cesarean delivery for HSV lesions and to

decrease neonatal viral exposure at the time of vaginal delivery.[47]

At this time, data are insufficient to recommend antiviral suppressive therapy to all asymptomatic HSV-2-seropositive pregnant women. However, after discussing the risks and benefits, antiviral suppressive therapy in the last trimester of pregnancy may be a reasonable option for these patients.

The recommended doses of antiviral medications for HSV suppression in the third trimester of pregnancy are shown in **TABLE 2.**

Avoid unnecessary invasive procedures in labor

Women with genital herpes but without lesions or symptoms at the time of labor may proceed with vaginal delivery. However, we recommend avoiding artificial rupture of membranes, fetal scalp electrodes, and vacuum or forceps delivery in these women except when these practices are critical to obstetrical care, as they appear to increase the risk of HSV transmission.[50]

Can we prevent HSV acquisition in pregnant women?

No guidelines address how to prevent HSV acquisition during pregnancy to decrease the incidence of neonatal herpes. However, we believe that to prevent neonatal HSV we need especially to prevent mothers from acquiring genital HSV in the third trimester of pregnancy. To do this, we need to identify women at risk of acquiring HSV in pregnancy. Routine HSV serologic testing of patients and their partners as part of prenatal counseling or during pregnancy may affect behavior and reduce acquisition of HSV in pregnancy. Studies of the impact of routine HSV serologic testing in pregnancy are under way.

For nonpregnant women of reproductive age who are sexually active, serologic testing for HSV should be included as part of screening for sexually transmitted diseases, as advised by the US Centers for Disease Control and Prevention. If a woman is seronegative, her partner can be tested to determine her risk of acquisition.

REFERENCES

1. **Fleming D, McQuillan G, Johnson R, et al.** Herpes simplex virus type 2 in the United States, 1976 to 1994. N Engl J Med 1997; 337:1105–1111.
2. **Stanberry L, Cunningham A, Mertz G, et al.** New developments in the epidemiology, natural history and management of genital herpes. Antiviral Res 1999; 42:1–14.
3. **Nahmias A, Lee F, Beckman-Nahmias S.** Sero-epidemiological and sociological patterns of herpes simplex virus infection in the world. Scand J Infect Dis 1990; 69:19–36.
4. **Leone P, Fleming DT, Gilsenan AW, Li L, Justus S.** Seroprevalence of herpes simplex virus-2 in suburban primary care offices in the United States. Sex Transm Dis 2004; 31:311–316.
5. **Brown ZA, Selke SA, Zeh J, et al.** Acquisition of herpes simplex virus during pregnancy. N Engl J Med 1997; 337:509–515.
6. **Kulhanjian J, Soroush V, Au D, et al.** Identification of women at unsuspected risk of primary infection with herpes simplex virus type 2 during pregnancy. N Engl J Med 1992; 326:916–920.
7. **Gardella C, Brown Z, Wald A, et al.** Risk factors for herpes simplex virus transmission to pregnant women: a couples study. Am J Obstet Gynecol 2005; 193:1891–1899.
8. **Bryson YJ, Dillon M, Bernstein DI, Radolf J, Zakowski P, Garratty E.** Risk of acquisition of genital herpes simplex virus type 2 in sex partners of persons with genital herpes: a prospective couple study. J Infect Dis 1993; 167:942–946.
9. **Ashley RL, Wald A, Eagleton M.** Pre-market evaluation of the POCkitTM HSV-2 type specific serologic test in culture-documented cases of genital herpes simplex virus type 2. Sex Transm Dis 2000; 27:266–269.
10. **Ashley RL, Wald A.** Genital herpes: review of the epidemic and potential use of type-specific serology. Clin Microbiol Rev 1999; 12:1–8.
11. **Mertz GJ, Benedetti J, Ashley R, Selke SA, Corey L.** Risk factors for the sexual transmission of genital herpes. Ann Intern Med 1992; 116:197–202.
12. **Mertz GJ, Schmidt O, Jourden JL, et al.** Frequency of acquisition of first-episode genital infection with herpes simplex virus from symptomatic and asymptomatic source contacts. Sex Transm Dis 1985; 12:33–39.
13. **Mertz GJ, Coombs RW, Ashley R, et al.** Transmission of genital herpes in couples with one symptomatic and one asymptomatic partner: a prospective study. J Infect Dis 1988; 157:1169–1177.
14. **Langenberg A, Corey L, Ashley R, Leong W, Straus S.** A prospective study of new infections with herpes simplex virus type 1 and type 2. N Engl J of Med 1999; 341:1432–1438.
15. **Wald A, Zeh J, Selke S, et al.** Reactivation of genital herpes simplex virus type 2 infection in asymptomatic HSV-2 seropositive persons. N Engl J Med 2000; 342:844–850.
16. **Fife KH, Bernstein DI, Tu W, et al.** Predictors of herpes simplex virus type 2 antibody positivity among persons with no history of genital herpes. Sex Transm Dis 2004; 31:676–681.
17. **Langenberg A, Benedetti J, Jenkins J, Ashley R, Winter C, Corey L.** Development of clinically recognizable genital lesions among women previously identified as having "asymptomatic" HSV-2 infection. Ann Intern Med 1989; 110:882–887.
18. **Roberts CM, Pfister JR, Spear SJ.** Increasing proportion of herpes simplex virus type 1 as a cause of genital herpes infection in college students. Sex Transm Dis 2003; 30:797–800.
19. **Ribes JA, Steele AD, Seabolt JP, Baker DJ.** Six-year study of the incidence of herpes in genital and nongenital cultures in a central Kentucky medical center patient population. J Clin Microbiol 2001; 39:3321–3325.
20. **Mertz GJ, Rosenthal SL, Stanberry LR.** Is herpes simplex virus type 1 (HSV-1) now more common than HSV-2 in first episodes of genital herpes? Sex Transm Dis 2003; 30:801–802.
21. **Lafferty WE, Downey L, Celum C, Wald A.** Herpes simplex virus type 1 as a cause of genital herpes: impact on surveillance and prevention. J Infect Dis 2000; 181:1454–1457.
22. **Wald A, Ericsson M, Krantz E, Selke S, Corey L.** Oral shedding of herpes simplex virus type 2. Sex Transm Infect 2004; 80:272–276.
23. **Engelberg R, Carrell D, Krantz E, Corey L, Wald A.** Natural history of genital herpes simplex virus type 1 infection. Sex Transm Dis 2003; 30:174–177.

24. **Wald A, Corey L, Cone R, Hobson A, Davis G, Zeh J.** Frequent genital HSV-2 shedding in immunocompetent women. J Clin Invest 1997; 99:1092–1097.
25. **Brown Z, Benedetti J, Watts D, et al.** A comparison between detailed and simple histories in the diagnosis of genital herpes complicating pregnancy. Am J Obstet Gynecol 1995; 172:1299–1303.
26. **Hensleigh P, Andrews W, Brown Z, Greenspoon J, Yasukawa L, Prober C.** Genital herpes during pregnancy: inability to distinguish primary and recurrent infections clinically. Obstet Gynecol 1997; 89:891–895.
27. **Frederick DM, Bland D, Gollin Y.** Fatal disseminated herpes simplex virus infection in a previously healthy pregnant woman. A case report. J Reprod Med 2002; 47:591–596.
28. **Young E, Chafizadeh, E, Oliveriara VL, Genta RM.** Disseminated herpesvirus infection during pregnancy. Clin Infect Dis 1996; 22:51–58.
29. **Kang H, Graves, CR.** Herpes simplex hepatitis in pregnancy: a case report and review of the literature. Obstet Gynecol Survey 1999; 54:463–468.
30. **Dupuis O, Audiber F, Fernandez H, Frydman R.** Herpes simplex virus encephalitis in pregnancy. Obstet Gynecol 1999; 94:810–812.
31. **Hollier LM, Scott LL, Murphree SS, Wendel GD, Jr.** Postpartum endometritis caused by herpes simplex virus. Obstet Gynecol 1997; 89:836–838.
32. **Hixson M, Collins JH.** Postpartum herpes simplex endometritis: A case report. J Reprod Med 2001; 46:849–852.
33. **Slomka MJ, Emery L, Munday PE, Moulsdale M, Brown DW.** A comparison of PCR with virus isolation and direct antigen detection for diagnosis and typing of genital herpes. J Med Virol 1998; 55:177–183.
34. **Cone R, Hobson A, Brown Z, et al.** Frequent detection of genital herpes simplex virus DNA by polymerase chain reaction among pregnant women. JAMA 1994; 272:792–796.
35. **Hobson A, Wald A, Wright N, Corey L.** Evaluation of a quantitative competitive PCR assay for measuring of HSV DNA in genital tract secretions. J Clin Microbiol 1997; 35:548–552.
36. **Wald A, Huang ML, Carrell D, Selke S, Corey L.** Polymerase chain reaction for detection of herpes simplex virus (hsv) dna on mucosal surfaces: comparison with hsv isolation in cell culture. J Infect Dis 2003; 188:1345–1351.
37. **Centers for Disease Control and Prevention.** Sexually transmitted diseases treatment guidelines 2002. MMWR Recomm Rep 2002; 51(RR-6):1–82.
38. **Roizman B, Sears A.** Herpes simplex viruses and their replication. In: Fields BN KD, Howley PM, Chanock RM, Melnick JL, Monath TP, Roizman B, editors. Virology. 3rd ed. Philadelphia: Lippincott-Raven; 1996:2231.
39. **Morrow RA FD.** Inaccuracy of certain commercial enzyme immunoassays in diagnosing gential infections with herpes simplex viurs type 1 or 2. Amer J Clin Pathol 2003; 120:839–844.
40. **Ashley R.** Performance and use of HSV type-specific serology test kits. Herpes 2002; 9:38–45.
41. **Saville M, Brown D, Burgess C, et al.** An evaluation of near patient tests for detecting herpes simplex virus type-2 antibody. Sex Transm Infect 2000; 76:381–382.
42. **Ribes JA, Hayes M, Smith A, Winters JL, Baker DJ.** Comparative performance of herpes simplex virus type 2-specific serologic assays from Meridian Diagnostics and MRL diagnostics. J Clin Microbiol 2001; 39:3740–3742.
43. **Eis-Hubinger AM, Daumer M, Matz B, Schneweis KE.** Evaluation of three glycoprotein G2-based enzyme immunoassays for detection of antibodies to herpes simplex virus type 2 in human sera. J Clin Microbiol 1999; 37:1242–1246.
44. **Prince HE, Ernst CE, Hogrefe WR.** Evaluation of an enzyme immunoassay system for measuring herpes simplex virus (HSV) type 1-specific and HSV type 2-specific IgG antibodies. J Clin Lab Anal 2000; 14:13–16.
45. **Ashley R, Cent A, Maggs V, Corey L.** Inability of enzyme immunoassays to discriminate between infections with herpes simplex virus type 1 and 2. Ann Intern Med 1991; 115:520–526.
46. **Morrow RA, Friedrich D, Meier A, Corey L.** Use of "biokit HSV-2 Rapid Assay" to improve the positive predictive value of Focus HerpeSelect HSV-2 ELISA. BMC Infect Dis 2005; 5:84.
47. **American College of Obstetricians and Gynecologists.** Practice bulletin. Management of genital herpes in pregnancy. 1999; Number 8, 1999. Int J Gynaecol Obstet 2000; 68:165Men>173.
48. **Bryson YJ, Dillon M, Lovett M, et al.** Treatment of first episodes of genital herpes simplex virus infections with oral acyclovir: a randomized double-blind controlled trial in normal subjects. N Engl J Med 1983; 308:916–920.
49. **Vontver LA, Hickok DE, Brown Z, Reid L, Corey L.** Recurrent genital herpes simplex virus infection in pregnancy: infant outcome and frequency of asymptomatic recurrences. Am J Obstet Gynecol 1982; 143:75–84.
50. **Brown ZA, Wald A, Morrow RA, Selke S, Zeh J, Corey L.** Effect of serologic status and cesarean delivery on transmission rates of herpes simplex virus from mother to infant. JAMA 2003; 289:203–209.
51. **Kimberlin DW.** Neonatal herpes simplex infection. Clin Microbiol Rev 2004; 17:1–13.
52. **Kimberlin D, Lin C-Y, Jacobs R, et al.** Natural history of neonatal herpes simplex virus infections in the acyclovir era. Pediatrics 2001; 108:223–229.
53. **Whitley R, Corey L, Arvin A, et al.** Changing presentation of herpes simplex virus infection in neonates. J Infect Dis 1988; 158:109–116.
54. **Whitley RJ, Roizman B.** Herpes simplex virus infections. Lancet 2001; 357:1513–1518.
55. **Brown ZA, Benedetti J, Ashley R, et al.** Neonatal herpes simplex virus infection in relation to asymptomatic maternal infection at the time of labor. N Engl J Med 1991; 324:1247–1252.
56. **Boucher FD, Yasukawa LL, Bronzan RN, Hensleigh PA, Arvin AM, Prober CG.** A prospective evaluation of primary genital herpes simplex virus type 2 infections acquired during pregnancy. Pediatr Infect Dis J 1990; 9:499–504.
57. **Sullivan-Bolyai JZ, Fife KH, Jacobs RF, Z M, Corey L.** Disseminated neonatal herpes simplex virusd type 1 from a maternal breast lesion. Pediatrics 1983; 71:455–457.
58. **Koelle DM, Benedetti J, Langenberg A, Corey L.** Asymptomatic reactivation of herpes simplex virus in women after first episode of genital herpes. Ann Intern Med 1992; 116:433–437.
59. **Whitley R, Arvin A, Prober C, et al.** Predictors of morbidity and mortality in neonates with herpes simplex infections. N Engl J Med 1991; 324:450–454.
60. **Braig S, Luton D, Sibony O, Elinger C, Boissinot C, Blot, Oury JF.** Acyclovir prophylaxis in late pregnancy prevents recurrent genital herpes and viral shedding. Eur J Obstet Gynecol Reprod Biol 2001; 96:55–58.
61. **Stray-Pedersen B.** Acyclovir in late pregnancy to prevent neonatal herpes simplex [letter]. Lancet 1990; 336:756.
62. **Scott LL, Sanchez PJ, Jackson GL, Zeray F, Wendel GD Jr.** Acyclovir suppression to prevent cesarean delivery after first-episode genital herpes. Obstet Gynecol 1996; 87:69–73.
63. **Brocklehurst P, Kinghorn G, Carney O, et al.** A randomised placebo controlled trial of suppressive acyclovir in late pregnancy in women with recurrent genital herpes infection. Br J Obstet Gynaecol 1998; 105:275–280.
64. **Scott LL, Hollier LM, McIntire D, Sanchez PJ, Jackson GL, Wendel GD, Jr.** Acyclovir suppression to prevent recurrent genital herpes at delivery. Infect Dis Obstet Gynecol 2002; 10:71–77.
65. **Watts DH, Brown ZA, Money D, et al.** A double-blind, randomized, placebo-controlled trial of acyclovir in late pregnancy for the reduction of herpes simplex virus shedding and cesarean delivery. Am J Obstet Gynecol 2003; 188:836–843.
66. **Sheffield JS, Hollier LM, Hill JB, Stuart GS, Wendel GD.** Acyclovir prophylaxis to prevent herpes simplex virus recurrence at delivery: a systematic review. Obstet Gynecol 2003; 102:1396–1403.
67. **Sheffield JS HJ, Laibl V, Hollier LM, Sanchez P, Wendel GD.** Valacyclovir suppression to prevent recurrent herpes at delivery: a randomized controlled trial [abstract]. Obstet Gynecol 2005; 104:5S.

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